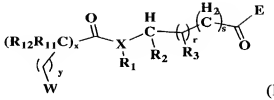
CLAIMS

We claim:

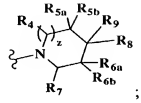
1. A compound according to formula (I),



(I),

or a pharmaceutically-acceptable salt, hydrate or prodrug thereof,

in which

E is  ;

X is N or CH;

R_1 is hydrogen or C_{1-6}alkyl or is taken together with R_2 or R_3 to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R_2 is hydrogen, aryl, cycloalkyl, heteroaryl, heterocyclo; or C_{1-6}alkyl or C_{2-6}alkenyl optionally substituted with one to three of hydroxy, alkoxy, halogen, cyano, nitro, trifluoromethyl, amino, alkylamino, aryl, cycloalkyl, heteroaryl, and/or heterocyclo; or R_2 is taken together with R_1 or R_3 to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R_3 is hydrogen or C_{1-6}alkyl or is taken together with R_1 or R_2 to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R_4, R_5, R_{5a} R_{5b}, R_6, R_{6a}, R_{6b}, and R_7 are independently selected from hydrogen, alkyl, substituted alkyl, halogen, hydroxy, alkoxy, keto, aryl, heteroaryl, cycloalkyl, and

heterocyclo, or R_{5a} and/or R_{5b}, R_{6a} and/or R_{6b}, are taken together with R_8 or R_9 to form a fused carbocyclic, heterocyclic or heteroaryl ring;

R_8 and R_9 are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, $-OR_{13}$, $-NR_{13}R_{14}$, $-SR_{13}$ $-S(O)_pR_{14}$, $-C(=O)R_{13}$, $-OC(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{14}$, $-NR_{13}C(=O)R_{14}$, $-OC(=O)NR_{13}R_{14}$, $-NR_{13}CO_2R_{14}$, $-NR_{13}C(=O)NR_{14}R_{15}$ or $-NR_{13}SO_2R_{14}$; or R_8 and R_9 taken together form a monocyclic or bicyclic cycloalkyl or heterocyclo joined in a spiro fashion to ring E at C*, provided that R_8 and R_9 are not both hydrogen, and provided further that when R_8 is $-OR_{13}$, $-(CH_2)_k$-aryl or $-(CH_2)_k$-heteroaryl, then R_9 is not $-C(=O)NR_{18}R_{19}$, $-CO_2R_{19}$, $-(CH_2)_mNR_{18}SO_2R_{20}$, $-(CH_2)_mNR_{18}C(=O)R_{20}$, $-(CH_2)_mOR_{19}$, $-(CH_2)_mO(C=O)R_{20}$, $-CH(R_{18})R_{19}$, or $-(CH_2)_mNR_{18}(C=O)NR_{19}R_{21}$;

R_{11} and R_{12} are selected independently of each other from hydrogen, alkyl, halogen, hydroxy, hydroxyalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl, cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, and where y is at least 1, then R_{11} and R_{12} may be heterocyclo or heterocycloalkyl, or R_{11} and R_{12}, when attached to the same carbon atom, may join to form a spirocycloalkyl ring;

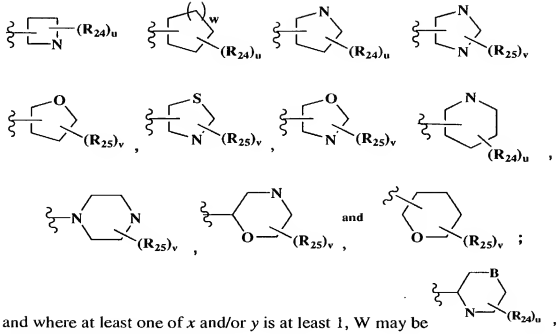
R_{13}, R_{14} and R_{15} are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heterocyclo, or heteroaryl; or R_{13} and R_{14}, or R_{14} and R_{15} may join together to form a heterocyclo or heteroaryl, except R_{14} is not hydrogen when joined to a sulfonyl group as in $-S(O)_pR_{14}$ or $-NR_{13}SO_2R_{14}$;

W is selected from:

2) $-NR_{16}R_{17}$, $-NR_{16}C(=O)R_{22}$, $-NR_{16}CO_2R_{22}$, $-OR_{23}$, amidino, and guanidino;

2) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl, pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein said heteroaryl and heterocyclo groups may be substituted or unsubstituted and may have an optionally-substituted carbocyclic, heterocyclic or heteraryl ring fused thereto; or

3) a ring selected from:



and where at least one of *x* and/or *y* is at least 1, W may be , wherein B is N, O or S;

R_{16} and R_{17} are selected from hydrogen, alkyl and substituted alkyl;

R_{18}, R_{19} and R_{21} are independently hydrogen or C_{1-6}alkyl optionally substituted with halogen;

R_{20} is C_{1-6}alkyl, aryl, or heteroaryl;

R_{22} and R_{23} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclo;

R_{24} and R_{25} at each occurrence are attached to any available carbon or nitrogen atom of W and at each occurrence are selected from hydrogen, C_{1-6}alkyl, halogen, substituted C_{1-6}alkyl, amino, alkylamino, cyano, nitro, trifluoromethoxy, $-C(=O)R_{26}$, $-CO_2R_{26}$, $-SO_2R_{26}$, $-OR_{26}$, aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or two R_{25} attached to two adjacent carbon atoms or adjacent carbon and nitrogen or carbon atoms may join to form a fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two R_{24} or two R_{25} when attached to the same carbon atom may form keto (=O);

R_{26} is hydrogen, alkyl, substituted alkyl, aryl, heterocyclo, cycloalkyl, or heteroaryl, except when joined to a sulphonyl group as in SO_2R_{26}, then R_{26} is not hydrogen;

k and *m* are independently 0, 1, 2 or 3;

p is 1, 2, or 3;

r is 0 or 1;

s is 0 or 1;

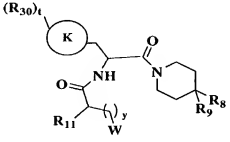
u and *v* are 0, 1, 2, or 3;

w is 0, 1, or 2;

x and *y* are 0, 1, 2, 3, or 4; and

z is 0, 1, or 2.

2. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, having the formula:



in which,

K is aryl or heteroaryl;

R_{30} is attached to any available carbon or nitrogen atom of K and is selected from C_{1-4}alkyl, hydroxy, alkoxy, halogen, nitro, cyano, amino, alkylamino, phenyl, and –C(=O)phenyl; and

t is 0, 1 or 2.

3. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

W is $-NR_{16}R_{17}$, $-NHC(=O)R_{22}$, $-NHCO_2$alkyl, OR_{23}, or azetidinyl;

R_{16} and R_{17} are independently selected from hydrogen, C_{1-8}alkyl, and $(CH_2)_q$-J, wherein J is selected from napthyl, furanyl, indolyl, imidazolyl, pyrimidinyl, benzothienyl, pyridinyl, pyrrolyl, pyrrolidinyl, thienyl, and C_{3-7}cycloalkyl, wherein the alkyl, alkylene, and/or J groups of R_{16} and/or R_{17} are optionally substituted with up to three R_{32};

R_{22} is selected from C_{1-6}alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl, phenyl, pyrollylalkyl, piperidinyl, and piperidinylalkyl, wherein R_{22} in turn is optionally substituted with one to two C_{1-4}alkyl and/or $-CO_2(C_{1-4}$alkyl);

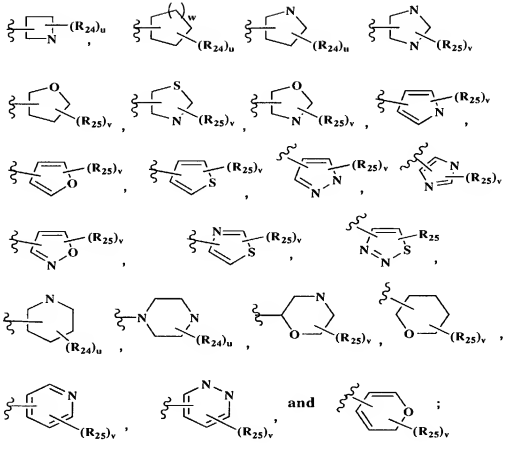
R_{23} is hydrogen or phenyl;

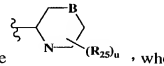
R_{32} is selected from C_{1-6}alkyl, hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, trifluoromethyl, halogen, phenyl, benzyl, phenyloxy, benzyloxy, $-C(=O)(CH_2)NH_2$, $-CO_2(C_{1-4}$alkyl), $-SO_2(C_{1-4}$alkyl), tetrazolyl, piperidinyl, pyridinyl, and indolyl, wherein when R_{32} is a ring, said ring in turn is optionally substituted with one to two C_{1-4}alkyl, hydroxy, methoxy, and/or halogen; and

q is 0, 1, 2 or 3.

4. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

W is a ring selected from:



and where at least one of *x* and/or *y* is at least 1, W may be  , wherein B is N, O or S;

R_{24} is selected from keto (=O), C_{1-6}alkyl, halogen, amino, aminoalkyl, alkylamino, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, –C(=O)alkyl, –C(=O)aminoalkyl, –C(=O)phenyl, –C(=O)benzyl, $-CO_2$alkyl, $-CO_2$phenyl, $-CO_2$benzyl, $-SO_2$alkyl, $-SO_2$aminoalkyl, $-SO_2$phenyl, $-SO_2$benzyl, phenyl, benzyl, phenyloxy, benzyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl, and each R_{24} in turn is optionally substituted with one to two R_{31};

R_{25} at each occurrence is attached to any available carbon or nitrogen atom of W and is selected from C_{1-6}alkyl, halogen, amino, aminoalkyl, alkylamino, hydroxy, C_1-

$_4$alkoxy, hydroxyC_{1-4}alkyl, –C(=O)alkyl, –C(=O)aminoalkyl, –C(=O)phenyl, –C(=O)benzyl, –CO_2alkyl, –CO_2phenyl, –CO_2benzyl, –SO_2alkyl, –SO_2aminoalkyl, –SO_2phenyl, –SO_2benzyl, phenyl, benzyl, phenyloxy, benzyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl, and/or two R_{25} when attached to adjacent carbon atoms may be taken together to form a fused benzo or pyrazolyl ring, and/or two R_{25} when attached to the same carbon atom (in the case of a non-aromatic ring) may form keto (=O), and each R_{25} in turn is optionally substituted with up to two R_{31};

R_{31} is selected from halogen, trifluoromethyl, C_{1-4}alkyl, hydroxy, and C_{1-4}alkoxy;

w is selected from 0, 1, or 2; and

u and *v* are selected from 0, 1, and 2.

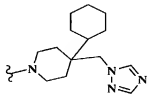
5. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

R_8 and R_9 are selected independently from hydrogen, alkyl, –$(CH_2)_j$-C(=O)alkyl, –$(CH_2)_j$-phenyl, –$(CH_2)_j$-napthyl, –$(CH_2)_j$-C_{4-7}cycloalkyl, –$(CH_2)_j$-heterocyclo, and –$(CH_2)_j$- heteroaryl, or R_8 and R_9 together form a spirocycloalkyl or spiroheterocyclic ring; and

j is selected from 0, 1, 2 and 3.

6. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

E is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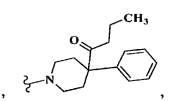
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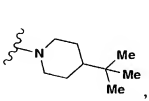
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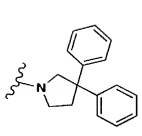

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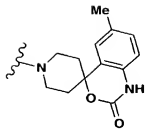

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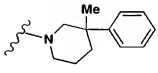

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7. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which

R_{11} and R_{12} are (i) at each occasion independently selected from:

a) hydrogen,

b) C_{1-6}alkyl,

c) C_{1-6}alkyl substituted with up to two of hydroxy, alkoxy, amino, alkylamino, imidazolyl, pyrazolyl, phenyl, napthyl, pyridinyl, indolyl, pyrimidyl, furyl, thiazolyl, and thienyl, wherein said ringed substituents in turn are optionally substituted with one to three R_{33} and/or have a benzene ring fused thereto optionally substituted with one to two R_{33};

d) C_{3-7}cycloalkyl optionally substituted with up to two R_{33} and/or having a benzene ring fused thereto, wherein said fused benzene ring is optionally substituted with up to two R_{33};

e) phenyl optionally substituted with up to three R_{33};

f) where *y* is at least one, R_{11} and R_{12} may also be selected from piperidinyl, pyrrolidinyl, piperidinylalkyl, and pyrrolidinylalkyl, in turn optionally substituted with up to three R_{33}; or

ii) alternatively, one of R_{11} and one of R_{12} attached to the same carbon atom may be taken together to form a spirocycloalkyl ring;

R_{33} is selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halogen, nitro, phenyl, benzyl, phenyloxy, benzyloxy, -C(=O)phenyl, amino, alkylamino, and aminoalkyl, wherein when R_{33} includes a phenyl group said phenyl group in turn is

optionally substituted with one to two of halogen, nitro, cyano, C_{1-4} alkyl, and/or C_{1-4} alkoxy.

8. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which

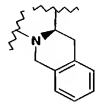
R_2 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, biphenyl, C_{2-6}alkenylene-K, and $-(CH_2)_g$-K;

K is selected from phenyl, napthyl, thienyl, thiazolyl, pyridinyl, pyrimidinyl, and C_{5-6}cycloalkyl, wherein each group K in turn is optionally substituted with one to three R_{30} or has a benzene ring fused thereto, which also may be substituted with one to three R_{30};

R_{30} is selected from C_{1-4}alkyl, hydroxy, alkoxy, halogen, nitro, cyano, amino, alkylamino, phenyl, and acylphenyl; and

g is 0, 1, 2 or 3.

9. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which $-X(R_1)-CH(R_2)-CH(R_3)_r-(CH_2)_s-$, taken together are selected from C_{1-4}alkylene,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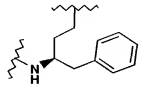
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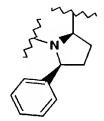
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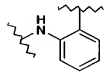
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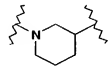
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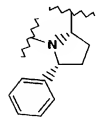
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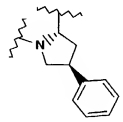
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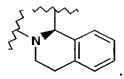
and  .

10. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which

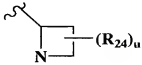
X is N;

R_1 is hydrogen or C_{1-4}alkyl;

r is 0; and

s is 0.

11. A compound according to claim 10, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

W is  , $-NR_{16}R_{17}$, $NR_{16}C(=O)R_{22}$, OH, or imidazolyl;

R_{16} and R_{17} are selected from hydrogen and C_{1-4}alkyl;

R_{22} is C_{1-4}alkyl, phenyl or piperidinylC_{1-4}alkyl;

R_{24} is C_{1-4}alkyl; and

u is 0 or 1.

12. A compound according to claim 11, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

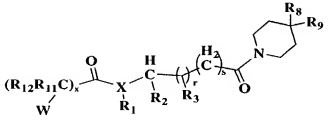
R_{11} is hydrogen, C_{1-4}alkyl, or imidazolylC_{1-4}alkyl; and

R_{12} is hydrogen or C_{1-4}alkyl.

13. A compound according to claim 1, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which R_{16} and R_{17} are independently selected from hydrogen, C_{1-}

$_8$alkyl, and C_{1-8}substituted alkyl, except R_{16} and R_{17} are not alkyl substituted with pyridiyl, imidazolyl, thiazolyl, pyrimidinyl, or piperazinyl, and W is not morpholinyl.

14. A compound according to the formula,



or a pharmaceutically-acceptable salt, hydrate or prodrug thereof,

in which

X is N or CH;

R_1 is hydrogen or C_{1-6}alkyl or is taken together with R_2 or R_3 to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R_2 is hydrogen, aryl, cycloalkyl, heteroaryl, or heterocyclo; or a C_{1-6}alkyl or C_{2-6}alkenyl optionally substituted with one to three of hydroxy, halogen, aryl, cycloalkyl, heteroaryl, and/or heterocyclo; or R_2 is taken together with R_1 or R_3 to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R_3 is hydrogen or C_{1-6}alkyl or is taken together with R_1 or R_2 to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R_8 and R_9 are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, $-OR_{13}$, $-NR_{13}R_{14}$, $-SR_{13}$ $-S(O)_pR_{14}$, $-C(=O)R_{13}$, $-OC(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{14}$, $-NR_{13}C(=O)R_{14}$, $-OC(=O)NR_{13}R_{14}$, $-NR_{13}CO_2R_{14}$, $-NR_{13}C(=O)NR_{14}R_{15}$ or $-NR_{13}SO_2R_{14}$; or R_8 and R_9 taken together form a monocyclic or bicyclic cycloalkyl or heterocyclo joined in a spiro fashion to ring E at C*,

R_{11} and R_{12} are selected independently of each other from hydrogen, alkyl, halogen, hydroxy, hydroxyalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl,

cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, or R_{11} and R_{12}, when attached to the same carbon atom, may join to form a spirocycloalkyl ring;

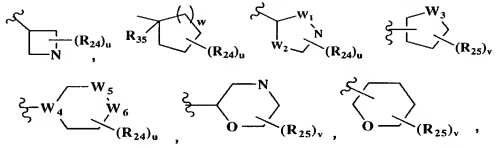
R_{13}, R_{14} and R_{15} are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heterocyclo, or heteroaryl; or R_{13} and R_{14}, or R_{14} and R_{15} may join together to form a heterocyclo or heteroaryl, except R_{14} is not hydrogen when joined to a sulfonyl group as in $-S(O)_pR_{14}$ or $-NR_{13}SO_2R_{14}$;

W is selected from:

3) $-NR_{16}R_{17}$, $-NR_{16}C(=O)R_{22}$, $-NR_{16}CO_2R_{22}$, or $-OR_{23}$; or

4) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl, pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein said heteroaryl and heterocyclo groups may be optionally substituted with one to three R_{36}, and may have an optionally-substituted carbocyclic, heterocyclic or heteraryl ring fused thereto; or

3) a carbocyclic, heterocyclic, or heteroaryl ring selected from:



in which W_1 and W_2 are NH, CH_2, O or S, W_3 is O or S, W_4 is N or CH, and W_5 and W_6 are NH or CH_2, wherein when W_1, W_2, W_5 and W_6 are NH or CH_2, said groups are optionally substituted with R_{24};

R_{16} and R_{17} are C_{1-8}alkyl or $(CH_2)_q$-J, wherein J is selected from aryl, heteroaryl, heterocyclo, and cycloalkyl, wherein the alkyl, alkylene, and/or J groups of R_{16} and/or R_{17} are optionally substituted with up to three R_{32};

R_{22} is selected from C_{1-6}alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl, phenyl, pyrollylalkyl, piperidinyl, and piperidinylalkyl, wherein R_{22} in turn is optionally substituted with one to two C_{1-4}alkyl and/or $-CO_2(C_{1-4}$alkyl);

R_{23} is hydrogen or aryl;

R_{24} and R_{25} at each occurrence are attached to any available carbon or nitrogen atom of W and at each occurrence are selected from hydrogen, C_{1-6}alkyl, halogen, substituted C_{1-6}alkyl, amino, alkylamino, $-C(=O)R_{26}$, $-CO_2R_{26}$, $-SO_2R_{26}$, $-OR_{26}$, aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or two R_{25} attached to two adjacent carbon atoms or adjacent carbon and nitrogen atoms may be taken together to form a fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two R_{24} or two R_{25} when attached to the same carbon atom may form keto (=O);

R_{26} is hydrogen, alkyl, phenyl, benzyl, or aminoalkyl, except when joined to a sulphonyl group as in SO_2R_{26}, then R_{26} is not hydrogen;;

R_{32} is selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, halogen, nitro, phenyl, benzyl, phenyloxy, benzyloxy, -C(=O)phenyl, amino, alkylamino, and aminoalkyl, wherein when R_{32} includes a phenyl group said phenyl group in turn is optionally substituted with one to two of halogen, nitro, cyano, C_{1-4} alkyl, and/or C_{1-4} alkoxy;

R_{35} and R_{36} at each occurrence is selected from C_{1-6}alkyl, halogen, substituted C_{1-6}alkyl, hydroxy, alkoxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, acyl, carboxyalkyl, sulfonyl, aryl, heteroaryl, heterocyclo, and cycloalkyl;

p is 1, 2 and 3;

r is 0 or 1;

s is 0 or 1;

u and *v* are 0, 1, or 2;

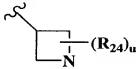
w is 0, 1, or 2; and

x is 0, 1, 2, 3, or 4.

15. A compound according to claim 14, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, in which

X is N;

R_1 is hydrogen or C_{1-4}alkyl;

W is  , $-NR_{16}R_{17}$, or $NR_{16}C(=O)R_{22}$;

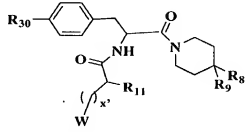
R_{24} is C_{1-4}alkyl;

r is 0;

s is 0; and

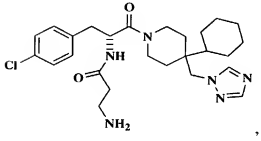
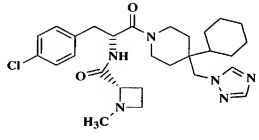
u is 0 or 1.

16. A compound according to claim 14, or a pharmaceutically-acceptable salt hydrate, or prodrug thereof, having the formula,



in which x' is 0, 1 or 2 and R_{30} is halogen or methoxy.

17. A compound according to claim 1, having the formula,

 ,  ,

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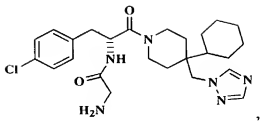
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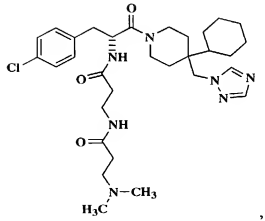
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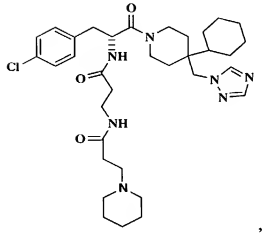
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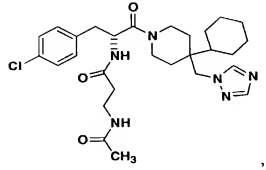
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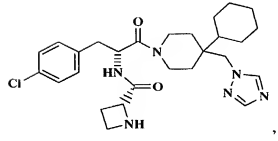
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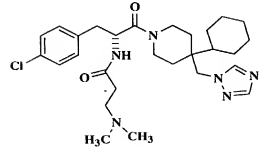
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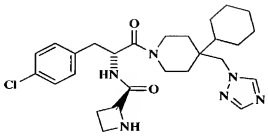
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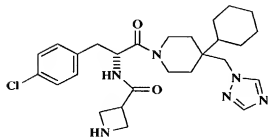
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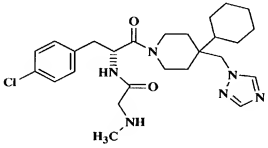
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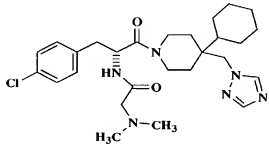
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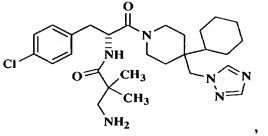
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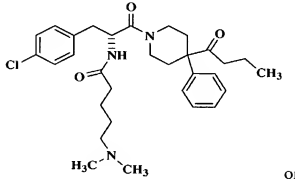
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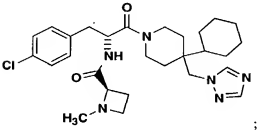
;

or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof.

18. A pharmaceutical composition comprising at least one compound according to claim 1 or a pharmaceutically-acceptable salt hydrate, or prodrug thereof; and a pharmaceutically-acceptable carrier or diluent.

19. A pharmaceutical composition comprising (i) at least one compound according to claim 1 or a pharmaceutically-acceptable salt hydrate, or prodrug thereof; (ii) at least one second compound effective for treating an inflammatory or immune disease, a cardiovascular disease, or neurodegenerative disorder; and (iii) a pharmaceutically-acceptable carrier or diluent.

20. The pharmaceutical composition according to claim 19 in which the at least one second compound comprises a phosphodiesterase inhibitor.

21. A method of treating a melanocortin-receptor associated condition, the method comprising administering to a warm-blooded species in need of such treatment a therapeutically-effective amount of at least one compound according to claim 1.

22. The method of claim 21 in which the melanocortin-receptor associated condition is an MC-1R or MC-4R associated condition.